The influence of opioids on gastric function: experimental and clinical studies

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experimental and clinical studies**

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Abstract

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After anesthesia and/or surgical procedures, gastrointestinal motility is commonly impaired. The causes are multifactorial, with surgical trauma, pain and perioperative drugs playing a major role. This thesis explores opioid effects on gastric motility in healthy volunteers and patients undergoing surgery.

Gastric emptying was studied by an absorption test (paracetamol method), and in healthy volunteers a remifentanyl infusion delayed gastric emptying. Body position altered emptying during the control situations, but not during the remifentanyl infusion. Further, two anesthetic methods were compared and no differences were found in immediate postoperative gastric emptying between a remifentanyl/propofol based intravenous anesthesia and an opioid free inhalational anesthesia, although the interindividual variability was high. Proximal gastric tone was studied using a gastric barostat. An infusion of remifentanyl caused two patterns of reaction regarding gastric tone, with half of the subjects increasing and half decreasing in gastric tone. Gastric myoelectrical activity was evaluated with electrogastrography (EGG), and a bolus dose of fentanyl caused a decrease in frequency of the gastric slow waves or disrupted this activity. However, the activity was unaffected in half of the investigated subjects. Analysis of polymorphisms (A118G and G691C) in the μ -opioid receptor gene was performed to find an explanation for the great interindividual variations seen in the barostat and EGG studies, but no association could be found.

These studies have shown that opioids have pronounced effects on gastric motility with variable individual responses that are difficult to predict. Polymorphisms in the μ -opioid receptor gene could not explain the variations. Postoperatively, other factors might contribute more than opioids to the impairment in gastric motility.

Keywords: gastrointestinal motility, gastric emptying, gastric tone, electrogastrography, analgesics, opioids, μ -opioid receptor, polymorphism

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Sammanfattning

Efter operation och anestesi får patienter ofta en negativ påverkan på magsäck och tarmar. Illamående och kräkningar är ett stort problem och många har svårt att komma igång med intag av föda och normal tarmfunktion då magsäcken och tarmarna "står stilla". Flera faktorer bidrar- bl.a. smärtan, det kirurgiska traumat och de läkemedel vi ger i samband med anestesi. Av de senare är opioider, d.v.s morfin och morfinliknande läkemedel, starkt bidragande. I detta avhandlingsarbete har opioiders effekter på magsäckens motilitet studerats.

Med ett absorptionstest (paracetamolmetoden) studerades hos frivilliga hur opioiden remifentanil påverkar magsäckstömning och om kroppspositionen har betydelse för tömningshastigheten ut i tarmen. Remifentanil fördröjde magsäckstömningen och under pågående opioid behandling hade kroppspositionen ingen större betydelse, vilket det däremot hade under kontrollförsöken. Med samma metod jämförde vi hos patienter två anestesimetoder och studerade magsäckstömning direkt efter en operation. Ingen skillnad kunde påvisas mellan en opioidbaserad och en opioidfri anestesi, men inom respektive grupp var det en stor variation i magsäckstömning mellan individerna.

Med en barostat studerades tonus i övre delen av magsäcken. Hos hälften av de frivilliga orsakade remifentanil en ökning av tonus och hos den andra hälften en minskning av tonus. Vidare undersöktes hos en grupp patienter opioiden fentanyl's påverkan på den elektriska aktiviteten i magsäcken. Med en elektrogastrograf (EGG) registrerades de långsamma elektriska vågor som koordinerar muskelrörelserna i magsäcken. Hos hälften av de undersökta påverkades aktiviteten av fentanyl med en sänkt vågfrekvens eller upphörande av vågor, medan aktiviteten var opåverkad hos den övriga hälften. För att finna en förklaring till variationen gjordes genetiska analyser av genen för opioidreceptorn hos de undersökta i barostat och EGG studierna. Variationer i genomet, s.k. polymorfism, var inte associerad till utfallen i studierna.

Studierna har visat på att opioider har en uttalad effekt på magsäckens motilitet och att den varierar kraftigt mellan individer. Polymorfism i genen för opioidreceptorn förklarade inte skillnaden mellan individer. Direkt efter operation bidrar sannolikt andra faktorer än anestesimetod till det variabla utfallet i magsäckstömning.

List of papers

The present thesis is based on the following papers, which will be referred to by their Roman numerals:

- I. **Wallden J, Thörn SE, Wattwil M.**
"The delay of gastric emptying induced by remifentanyl is not influenced by posture"
Anesthesia Analgesia. 2004 Aug;99(2):429-34
- II. **Wallden J, Thörn SE, Löqvist Å, Wattwil L, Wattwil M.**
"The effect of anesthetic technique on early postoperative gastric emptying: comparison of propofol-remifentanyl and opioid-free sevoflurane anesthesia".
Journal of Anesthesia 2006;20(4):261-7.
- III. **Wallden J, Thörn SE, Lindberg G, Wattwil M.**
"Effects of remifentanyl on gastric tone"
Submitted
- IV. **Wallden J, Lindberg G, Sandin M, Thörn SE, Wattwil M.**
"Effects of fentanyl on gastric myoelectrical activity – a possible association to polymorphisms of the μ -opioid receptor gene"
Accepted for publication in Acta Anaesthesiologica Scandinavica.

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Abbreviations

ASA-class	American Society of Anesthesiologists: Physical Status Classification system
AUC	Area under the curve
CNS	Central nervous system
CO ₂	Carbon dioxide
EGG	Electrogastrography
ENS	Enteric nervous system
GE	Gastric emptying
GI	Gastro intestinal
ICC	Interstitial cells of Cajal
ICU	Intensive care unit
I.V.	Intravenous
LHD	Left lateral head-down position
MMC	Migrating motor complex
MNTX	Methylnaltrexone
MOR	μ-opioid receptor
NANC	non-adrenergic non-cholinergic
OPRM1	μ-opioid receptor 1
POI	Postoperative ileus
PONV	Postoperative nausea and vomiting
RHU	Right lateral head-up position
TCI	Target controlled infusion
TIVA	Total intravenous anesthesia
VAS	Visual analogue scale

Allt vad Gud har gjort är skönt i rätta stunden. Han låter människor urskilja ett sammanhang, men aldrig kan de fatta Guds verk från början till slut.

Predikaren 3:11

To Maria and Andreas

Contents

Introduction	15
Normal gastric motility	15
<i>Myoelectric activity</i>	16
<i>Neuronal control</i>	16
<i>Gastric tone</i>	17
<i>Gastric emptying</i>	18
Methods for measuring gastric motility	18
Opioid drugs	18
<i>Fentanyl</i>	19
<i>Remifentanyl</i>	19
Effect of opioids on gastrointestinal motility.....	19
<i>Role of endogenous opioid peptides</i>	20
Anesthetic drugs and gastric motility	21
<i>Effects of volatile agents on gastrointestinal motility</i>	21
<i>Effect of propofol on gastrointestinal motility</i>	21
Prokinetic drugs.....	21
<i>μ-Opioid receptor antagonists</i>	22
Gastrointestinal motility during the perioperative period and intensive care	23
<i>Preoperative fasting</i>	23
<i>Early oral intake</i>	23
<i>Postoperative ileus</i>	23
<i>Postoperative nausea and vomiting (PONV)</i>	24
<i>Intensive Care</i>	24
Genetic variability	24
Aims of the thesis	27
Materials	29
Study I.....	29
Study II.....	29
Study III	29
Study IV	29
Methods	31
Gastric emptying (I-II)	31
Gastric tone (III)	31
Electrogastrography (IV)	32
Genetic Analysis (III-IV)	33
<i>DNA collection and purification.</i>	34
<i>Genotyping.</i>	34

Procedure	34
<i>Study I</i>	34
<i>Study II</i>	35
<i>Study III</i>	36
<i>Study IV</i>	37
Statistics	37
Results	39
Gastric emptying during an infusion of remifentanil and the influence of posture (I)	39
Immediate postoperative gastric emptying after total intravenous remifentanil-propofol based anesthesia (II).	39
Gastric tone after injection of glucagon (III)	41
Gastric tone during an infusion of remifentanil (III)	41
Electrogastrography (IV)	42
Genetic study (III-IV)	43
PONV (I-IV), other side effects (I-IV) and postoperative pain (II).	43
Discussion	45
The Paracetamol method	45
Gastric barostat	46
Electrogastrography (EGG)	47
Genetic testing	48
Gastric emptying during a remifentanil infusion and influence of posture (I)	48
Gastric emptying after opioid based vs opioid free anesthesia (II)	48
Effects of remifentanil on gastric tone (III)	49
Effects of fentanyl on gastric myoelectrical activity (IV)	51
Associations to genetic factors (III, IV).	53
Side effects of opioids	54
Future perspectives	54
Conclusions	55
Acknowledgments	56
References	57

Introduction

Why, as an anesthesiologist, am I writing a thesis about the gastrointestinal tract? Shouldn't I be more interested in the brain and the nerves? As a matter of fact, the stomach and the intestines play a major role during the perioperative period. The aim of preoperative fasting is an empty stomach at the start of anesthesia in order to reduce the risk of pulmonary aspiration. Postoperative nausea and vomiting (PONV), often termed "the big little problem", is a major concern. Postoperative ileus (POI) due to impairments in gastrointestinal motility is common, and it delays the start of oral feeding and the passage of stool. Patients sometimes rate gastrointestinal symptoms as more severe than postoperative pain, and impairment of gastrointestinal function often delays discharge from the hospital. To answer the initial question, the gastrointestinal tract is of central importance for both perioperative care and the anesthesiologist. Many factors contribute to the impairment of perioperative gastrointestinal function (1-4), and the opioid analgesics are one of the major contributors (5, 6).

The overall objective of this work was to acquire more knowledge about the mechanism and physiology behind opioid effects on the gastrointestinal system. The current understanding in the field is limited and much more research is needed (7). In this thesis I have explored the effects of two opioid drugs, fentanyl and remifentanyl, on gastric motility.

Normal gastric motility

The physiological functions of the stomach are to receive ingested food, mix it with secretions, mechanically break down the contents and finally pass the contents to the duodenum (2). The proximal stomach, the fundus, functions as a reservoir and with volume loads, muscles are adapted for maintaining a continuous contractile tone (8). The distal antral region exhibits phasic and peristaltic contractile activity and functions both as a pump and a grinding mill (9). The tone of the pyloric sphincter regulates the outflow to the duodenum (10).

Two patterns of gastric motility can be distinguished – fasting and postprandial motility. Fasting motility has a housekeeping function and consists of recurrent contractile activity, sweeping contents distally in the bowel (11). This pattern is described by the expression "migrating motor complex" (MMC), which is characterized by three different phases. MMC phase I starts approximately 2-3 hours after a meal, lasts for 1 hour, and during this phase there are only a few

contractions every 5 minutes. In MMC phase II, the frequency of contractions increases, but they are irregular. Phase III starts after a further 30 minutes, lasts for about 10 minutes, and the coordinated contraction is maximal with clear propagation of intraluminal contents. The interdigestive pattern terminates abruptly after ingestion of food. After a meal, the motility pattern is dependent on the physical state and nutrient content. The stomach exhibits submaximal and phasic contractile activity, similar to MMC phase II. The contents are mixed, digested and portioned out to the duodenum through the pylorus.

Myoelectric activity

Gastric smooth muscles display a rhythmic electrical activity, slow waves, with a frequency of approximately 3 cycles per minute. These slow waves originate from a gastric pacemaker region in the corpus region of the stomach and propagate towards the pylorus. With influence of the enteric nervous system and other regulatory mechanisms, the slow waves trigger the onset of spike potentials, which in turn initiate coordinated contractions of the gastric smooth muscles (12). Gastric motility and emptying depend on these slow waves.

Neuronal control

Neural networks for control of gastric motility are present both on the enteric and the central levels. The enteric nervous system (ENS) is a separate division of the autonomic nervous system and has local circuits for integrative functions independent of extrinsic nervous control. Many of the reflexes, “programs” and information processing for motility are located within the ENS. However, the functional physiology of the stomach is dependent on higher levels of control. (13)

The parasympathetic vagus nerve is a mixed sensory and motor nerve with 90% afferent fibers, transmitting sensory information to the brainstem, and 10% efferent fibers with motor functions (14). In the brainstem, the sensory neurons are located in the nucleus tractus solitarius (NTS) and the motor neurons are located in the dorsal motor nucleus of vagus (DMV). The two nuclei are in proximity to one another and there are dense networks of interneurons between them, providing sensory information for the motor output, and completing the vago-vagal reflex loop. The whole complex is also under the influence of higher centers and circulating hormones (15, 16). There are two subgroups of the efferent motor nerves, and the neurons are organized separately within the DMV

(16). Cholinergic fibers mediate excitations and non-adrenergic non-cholinergic (NANC) inhibition to the stomach.

The sympathetic innervations to the stomach originate from the thoracic spinal cord (T6 to T9). They consist of efferent adrenergic fibers and act mainly through inhibition of the cholinergic transmission in the stomach (17). Together with sympathetic afferent sensory fibers, the inhibiting gastro-gastric reflex is formed (18).

The composition of the contents in the intestines also affects motility. Lipids, carbohydrates, amino acids, low pH and hyperosmolarity in the duodenum inhibit gastric motility. The “ileal break”, activated by caloric content in the ileum, inhibits gastric motility and the glucagon-like peptide-1 (GLP-1) is the proposed mediator (19). Colonic distension decreases gastric tone (20).

Several endogenous substances are involved in the integrative functions. *Cholecystokinin*, released in the ileum in the presence of fatty contents, inhibits gastric emptying mainly through activation of afferent vagal fibers (21). *Ghrelin*, a relatively newly discovered gastric peptide, stimulates appetite, food intake and gastric motility (22). *Somatostatin*, released from D-cells found throughout the gastrointestinal tract, has complex actions on motility (21). *Motilin*, produced in the duodenum, stimulates stomach motility through direct activation of motilin receptors on enteric neurons, leading to activation of cholinergic neurons in the antral region of the stomach (23).

Gastric tone

The proximal part of the stomach acts as a reservoir and exhibits a constant dynamic tone. It adapts for volume loads, and volume waves portion contents to the distal part of the stomach. The tone is mainly controlled by the autonomous nervous system. (8, 18)

Tone is not equivalent to pressure. Gastric tone can be expressed as the length of the muscle fibers in the proximal stomach. As there is an adaptive relaxant reflex, a volume load might maintain the same intragastric pressure. Therefore, an almost empty stomach and a full stomach are able to have the same intragastric pressure, but different tone.

Gastric emptying

Gastric emptying (GE), the functional outcome of gastric emptying, is dependent on the character of the stomach contents. The emptying of liquids starts immediately and follows an exponential profile, meaning that a certain *proportion* of the liquids is emptied during each time interval. Usually the time for emptying half of the liquid contents is about 15-20 minutes. In contrast, any caloric content or solids in the food causes a change from the liquid pattern of emptying. For solid food, there is first a delay in emptying, a so-called lag-phase, where no contents are passed to the duodenum. Contents are then mixed, grinded and digested. This lag-phase lasts up to 1 hour and is followed by an emptying that is characterized as linear, as a certain *amount* of contents is emptied during each time interval (24). Posture influences gastric emptying, particularly with long emptying when patients are in a left lateral position (25-27) .

Methods for measuring gastric motility

Gastric emptying rates can be estimated with various methods. The “gold standard” is scintigraphic methods with radionuclide labeled test meals (28). With ultrasound techniques, transpyloric flow and gastric volumes can be estimated (29-31). Absorption tests, i.e. the paracetamol method, (32-34), and hydrogen breath tests (35) measure gastric emptying indirectly. Gastric pressures are studied with manometry catheters and gastric myoelectric activity with cutaneous electrogastrography (36). The gastric barostat measures proximal gastric tone (37).

Opioid drugs

Morphine-like alkaloids have been used for centuries for analgesia and sedation. Morphine was isolated from the opium flower in the beginning of the 19th century, and some half century later, with introduction of the needle and syringe in clinical practice, morphine could be administered in a controlled manner. Opioid drugs are still fundamental in the treatment of severe pain, and morphine is the reference substance to which other opioids are compared. Numerous analogues with various pharmacological profiles have been developed. (38)

Opioids mediate their effect via opioid receptors on cell membranes. Currently, five classes of receptors are identified, but research in humans has focused on the role of μ -, κ -, and δ -opioid receptors (39). All three receptor classes are expressed throughout the nervous systems, including the GI tract, and they partly overlap in distribution and function. The receptors bind to both exogenous opioids, i.e. morphine, and endogenous opioid peptides. (40, 41). The receptors differ in their

pharmacological profiles and have selectivity for the three classes of endogenous opioid peptides. Analgesia, as well as many of the side effects, are mainly mediated via activation of the μ -opioid receptor (MOR) (42, 43).

Morphine-analogue drugs exhibit their actions mainly through the MORs (44). MORs are widely distributed on cell membranes in the body and are present in the central nervous system (45-47) including at the spinal level (48), on peripheral nerves (49), and in the gastrointestinal tract (41, 50-52).

On the cellular level, the MOR is coupled to transmembrane G-proteins. The cellular effects involve hyperpolarizations of the cell membrane via K^+ and Ca^{++} channels and changes in the second messenger systems (i.e. cAMP, IP3). The physiological result of receptor activation depends on the site of action, but synaptic transmission is usually inhibited, i.e. via inhibition of presynaptic excitatory transmitter release or postsynaptic hyperpolarization (38).

Fentanyl

Fentanyl is the most common opioid used in daily anesthetic practice. It is a MOR agonist with analgesic potency 100 times that of morphine. It is highly lipophilic and has a high volume of distribution. It is usually given as repetitive bolus injections during anesthesia. Clearance from the body can be long, especially after repetitive doses. (53)

Remifentanyl

Remifentanyl is a MOR agonist with analgesic potency similar to that of fentanyl. It has a rapid onset and recovery and is usually administered as a continuous infusion. Remifentanyl is metabolized by unspecific esterases in the body, has a relatively small volume of distribution, and has a systemic half life of about 10 minutes. The context sensitive halftime (time to reduce the effect site concentration to 50%) is around 4 minutes and is independent of infusion time. This gives remifentanyl the unique property that after termination of a several hour long infusion, such as during anesthesia, remifentanyl is rapidly cleared and patients recover within minutes. Remifentanyl is used routinely today in anesthetic management. (54)

Effect of opioids on gastrointestinal motility

In 1917, Trendelenburg was the first to demonstrate the inhibitory effects of opioids on motility in an experimental setting using isolated animal intestines (55, 56). Since then, effects of opioids on gastrointestinal motility have been studied

extensively, but the mechanism is complex and still uncertain (7). Opioid receptors are widely spread in the gastrointestinal tract and are located on neurons in the ENS, on secretomotor neurons and on smooth muscles (57-60). Opioid receptors mediate the action of both exogenous opioids and endogenous opioid peptides, and generally speaking opioids suppress neural excitability through the opening of potassium conductance channels, leading to hyperpolarizations of cell membranes. Opioids affect a variety of functions including motility (41, 51, 52, 61-65) and secretion (57), and both μ - and κ -receptors are involved (40).

Opioid effects on motility can be both excitatory and inhibitory. The stomach and the intestines are under tonic inhibitory influence from neuronal networks controlling the coordinated contraction and propulsions. When opioids inhibit these inhibitory neurons, control from the neuronal network is released and an uncoordinated non-propulsive contraction occurs (57). This is seen, for example, when opioids induce a phase III-like activity in the antroduodenal region and disturb gastric motility (66). The negative effect is seen even with low doses of an opioid (67).

There is clear evidence that there is both a peripheral and a central mechanism in the inhibition of gastrointestinal motility (57, 66, 68). Higher centers involved in the regulation of gastrointestinal motility also express MORs (46, 69, 70). Opioid receptors are also present on afferent vagal nerve endings projecting to the NTS (47, 71, 72).

Role of endogenous opioid peptides

Endogenous opioid peptides (enkephalins, β -endorphins and dynorphines) are located within the GI tract. The function of these peptides is poorly understood, but they might play a role in the normal control of motility. The distribution of enkephalinergic neurons is closely matched to neurons expressing MOR (73). There is evidence that endogenous opioids are released during stress and trauma and inhibit the normal patterns of motility. After binding to ligands, the MOR receptor complex is usually internalized into the cell through endocytosis (41). Using immunohistochemical methods to demonstrate internalized opioid receptors, the release of endogenous peptides can be studied. In an animal model, abdominal surgery with and without manipulation of the intestines was associated with endogenous peptide release, while anesthesia alone was not. (74)

Inhibition of endogenous peptides, i.e. through blockage of opioid receptors, might therefore act prokinetically under conditions of disrupted motility (75).

Anesthetic drugs and gastric motility

Effects of volatile agents on gastrointestinal motility

There are only a few published studies on volatile agents and gastrointestinal motility and no studies regarding sevoflurane. Marshall et al showed (76) that halothane depressed motility of the stomach, jejunum and colon in dogs and that activity returned promptly after the agent was withdrawn. In rodents, halothane and enflurane had profound but different effects on motility (77). Both agents reduced the frequencies of the slow waves. Halothane reduced phase III activity in duodenum, intestinal motor activity was slowed after anesthesia, and contractile activity was affected. Enflurane increased the frequency of MMC during anesthesia, the frequency slowed to a normal rate after anesthesia, and there were no major effects on contractile activity. In humans, enflurane and halothane depress antral motility and reduce phase II activity (78). To summarize, volatile anesthetics affect gastric motility, but the effect may cease quickly after termination of the agents.

Effect of propofol on gastrointestinal motility

Propofol in low doses does not influence gastric motility (79), but there is evidence that propofol may inhibit motility in higher doses. In a laboratory setting, propofol inhibited spontaneous contractions in human gastric tissue (80).

Prokinetic drugs

Prokinetic drugs can be used to improve and restore gastrointestinal motility. Available major drug classes with prokinetic properties include antidopaminergic agents, serotonergic agents and motilin-receptor agonists. However, the drugs show signs of moderate prokinetic effects with adverse effects, and research on novel substances is currently intense. (81, 82)

Metoclopramide is a dopamine receptor antagonist that has been used for decades. As dopamine inhibits gastric motility (83, 84), blockade of the dopamine-2 receptor (D2) promotes motility. It is also suggested that metoclopramide has effects on serotonergic receptors. Metoclopramide is widely used in clinical practice, but the prokinetic effects last for only a short time. Also, the side effects are considerable, as all D2 receptor antagonists might induce extrapyramidal symptoms. *Domperidone* has properties that are similar to those of

metoclopramide, although the most common side effect is hyperprolactemia. The substance is available in many European countries, but currently not in Sweden.

Tegaserode is a novel serotonergic agent undergoing clinical evaluation. It is a partial 5-HT₄ receptor agonist and 5-HT_{2b} receptor antagonist (85) and accelerates orocecal transit in volunteers. It has not been associated with serious side effects. *Cisapride* is a 5-HT₄ receptor agonist with prokinetic actions in major parts of the gastrointestinal tract, including the stomach. It stimulates antral and duodenal contraction and improves gastric emptying. However, the substance was associated with severe cardiac arrhythmias and was withdrawn from the market in 2001.

The macrolide antibiotic *erythromycin* is a motilin receptor agonist and it initiates MMC phase III, and stimulates motility and gastric emptying through direct effects in the stomach. Compared to other prokinetic drugs, erythromycin is considered effective. Novel motilin receptor agonists with higher potency and without antibacterial activity are under development (86, 87).

μ-Opioid receptor antagonists

The classical μ -opioidreceptor antagonist *naloxone* improves opioid induced bowel dysfunction (88), but as the reversal also antagonizes the analgesic effect of opioids, the use of naloxone is limited (89).

Research in recent decades has focused on the development of peripheral μ -receptor antagonists that do not penetrate the blood-brain barrier. Hence, analgesic effects of opioids are maintained while gastrointestinal effects are antagonized. *Alvimopan* is a selective opioid antagonist with extremely limited oral absorption, and when given orally it does not cross the blood-brain barrier (39, 90, 91). Clinical phase III trials have showed that Alvimopan accelerates gastrointestinal recovery after abdominal surgery without compromising opioid based analgesia (92-96). *Metylnaltrexone* (MNTX), a derivate of naltrexone, is a peripheral opioid receptor antagonist that does not cross the blood brain-barrier and can be administered by both the oral and the intravenous route (97-99). MNTX is still under investigation in late clinical trials focusing on opioid induced obstipation (100). In patients treated with opioids, MNTX reduces orocecal transit time, induces laxation and is well tolerated (100, 101).

Gastrointestinal motility during the perioperative period and intensive care

Preoperative fasting

One of the most important preparations for patients before anesthesia and surgery is an empty stomach. Protective reflexes are abundant during anesthesia, and if regurgitation or vomiting occurs, contents from the stomach might be aspirated into the lungs, causing fatal aspiration pneumonitis (102). Previously, NPO (nil per os) after midnight was a rule, but research during the past 20 years has changed this dogma (103). Current guidelines state a two-hour fast for fluids and a six-hour fast for solids in healthy patients undergoing elective procedures (104-107). However, a spectrum of conditions like trauma, pain, emergency procedures, diabetes and opioid medication are associated with impaired gastric motility. If the stomach is not considered empty, special procedures are used routinely for rapidly protecting the airway during the induction of anesthesia (108).

Early oral intake

Today an early start of oral intake after anesthesia and surgery, sometimes within hours, is common. However, while there is currently no evidence that early intake diminishes the duration of postoperative ileus, the routine is not associated with adverse effects, except an increased risk of nausea (109-112). As opioids given perioperatively might have residual effects during recovery, this might delay the start of oral intake. Optimizing opioid administration might therefore be beneficial.

Postoperative ileus

Postoperative ileus (POI) is a transient bowel dysmotility that occurs following abdominal surgery (1, 113). It encompasses delayed gastric and colonic emptying and failure in the propulsion of the intestinal contents due to atonic bowel (2), and generally lasts for several days. Inhibitory neural reflexes, neurotransmitters, inflammatory mediator release and endogenous and exogenous opioids contribute to the pathogenesis (5). Activation of nociceptive afferent nerves and sympathetic inhibitory efferent nerves through the spinal reflex is believed to play a major role (18, 114). Blockade of these nerves with an intra- and postoperative epidural with local anesthetic reduces gastrointestinal paralysis and enhances recovery by up to 36 hours compared to analgesia with systemic opioids (115). Recent studies have shown that the prolonged phase of POI is caused by an enteric molecular inflammatory response in the segments of the intestines manipulated during surgery (1). Opioid receptors are also up-regulated with the inflammatory response (49) and might contribute to the impairment.

Postoperative nausea and vomiting (PONV)

PONV occurs commonly after anesthesia and is described as the “big little problem”. Patients often recall PONV as their worst experience after undergoing a surgical procedure. The etiology is multifactorial, and non-smokers, female gender, history of PONV or motion sickness and the use of opioids are associated with increased risks (116). The emetic center in the brainstem is in the proximity of the NTS and DMV. Nausea and vomiting induce changes in gastric motility through central mechanisms, but there is currently no evidence that motility changes in the stomach *per se* induce PONV. However, factors that induce motility changes also induce PONV. Therefore, it might be difficult to perform studies in humans where the aim is to study if an intervention with isolated gastric effects affects nausea and vomiting.

Intensive Care

In critical illness, impaired gastric motility is common and is associated with serious consequences. The underlying mechanisms are tissue ischemia, disturbances in fluid-electrolyte balance, abdominal surgery, infections and medications (i.e. opioids, catecholamines, anticholinergics) (117). The clinical picture includes enteral feeding intolerance, gastric retention, and paralytic ileus, and about 50% of intensive care unit (ICU) patients have delayed gastric emptying. As early enteral administration of nutrition is considered the best practice, with improved outcome in morbidity and mortality, efforts have been made to promote gastric motility in the critically ill (118). Erythromycin and metoclopramide are the most commonly used prokinetics in the ICU (119). With advantage to erythromycin, (120) both drugs improve gastric emptying (121, 122). Gastric emptying is even more improved if the two drugs are combined (123). However, rapid tachyphylaxis occurs frequently and limits the use of these two drugs (118). The use of enteral naloxone has been popular in many ICUs, but at this time there is only weak evidence in the literature. Meissner found that naloxone reduced gastric residual volumes and the frequency of pneumonia (124), and Mixides showed that enteral feeding was better tolerated with naloxone (125). Novel prokinetics are under evaluation for the ICU setting (126).

Genetic variability

In recent years research regarding individual variability in opioid-mediated analgesia and in side-effects has suggested an association with genetic disposition. Genetic variations might alter drug effects through changes in metabolizing enzymes, transport proteins and expression of cellular receptors. Recently, several

studies have focused on single nucleotide polymorphism (SNP) in the gene coding for the μ -opioid receptor (127-131).

Polymorphisms and mutations are variations of the normal "wildtype" genetic expression. If the variant is common in the population (>1%), it is termed *polymorphism*, and if it is rare (<1%) it is termed *mutation*. A single nucleotide polymorphism (SNP) occurs when a position in the DNA strand has two alternative nucleotides. As all chromosomes exist in pairs, a subject is *heterozygote* for a SNP if one of the genes carries the variant, and *homozygote* if both genes are variants.

One of the most common SNPs in the MOR gene is a change in the nucleotide base of A>G at position 118 (A118G). This results in an amino acid exchange from asparagine > aspartate at position 40 (Asn40Asp) in the receptor (127, 131). The expected frequencies in populations of heterozygous A118G and homozygous subjects are 20 and 2 %, respectively, and there are substantial variations between ethnic groups (132, 133).

The A118G alteration results in a loss of a putative glycosylation site of the receptor (134). Investigators report up to 3 times higher affinity to beta-endorphins for the variant (132), altered signal transduction pathways, and lower thresholds for morphine in neurone models (135). In contrast, others have reported no differences in ligand-binding or dose in the cellular response with the variant (136). The differences might be explained by the use of different cell lines.

Subjects carrying the A118G variant have a diminished pupillary response to the morphine metabolite morphine-6-glucuronide (M6G) (137). Observations in patients with renal failure (causes accumulation of M6G) indicate that the variant decreases side effects and the potency of M6G. There have been speculations about an M6G toxicity protection by the A118G variant (137). Others report that analgesic response to M6G is diminished in variants, while respiratory response (depression) is unchanged (138).

In experimental settings, A118G carriers have a higher threshold for pain (139). Clinical studies reveal decreased postoperative sensitivity to morphine after knee arthroplasty (140), carriers of A118G required more morphine for alleviation of pain caused by malignant disease (141), while there were no differences in opioid consumption after abdominal hysterectomy (142). After abdominal surgery there

was a tendency toward higher morphine consumption with the variant (143). Interestingly, there is speculation about an association with opioid induced nausea and vomiting, as carriers of the variant had less symptoms after exposure to M6G (144). Compared to a control group, patients switching to alternative opioids from morphine due to intolerance did not differ in the MOR gene (145).

The SNP A118G has also been explored in the context of substance addictions. Regarding alcohol intake, carriers of the variant had a higher sensitivity to alcohol, became more stimulated and sedated than normal “wildtypes” (146), and also had a stronger urge to drink more (147). Naltrexone, an opioid receptor antagonist, blunted the alcohol effect more in subjects with the variant (148). Some investigators report an association between alcohol dependence and the variant (146, 149, 150). However, a recent meta analysis concluded that there was no evidence for such an association (151).

Opioid systems are also believed to inhibit the hypothalamic-pituitary-adrenal axis (HPA-axis). A blockade of this opioidergic effect releases cortisol. In response to the MOR antagonist naloxone, the cortisol response was higher among carriers of the variant (152).

Aims of the thesis

- To study effects of the opioid remifentanil on gastric emptying and evaluate if extreme postures affect gastric emptying.
- To compare postoperative gastric emptying between a remifentanil-propofol based total intravenous anesthesia and an opioid free sevoflurane inhalational anesthesia.
- To study effects of remifentanil on proximal gastric tone using a gastric barostat.
- To study effects of fentanyl on gastric myoelectric activity using a cutaneous multichannel electrogastrograph (EGG).
- To test the hypothesis that single nucleotide polymorphisms (SNP) in the μ -opioid receptor gene are associated with the variable effects on gastric motility caused by opioids.

Materials

All studies were approved by the Ethics Committee of Örebro County Council (prior to 2004) and the Uppsala Regional Ethical Review Board (after 2004). Study II was also approved by the Swedish Medical Product Agency. All studies were performed at Örebro University Hospital, Örebro, Sweden, during the period 2000-2005.

Study I

Ten healthy male volunteers (ASA-class I-II) with a mean age of 23.9 years (range, 21-31) underwent four gastric emptying studies on four separate days.

Study II

Fifty patients (ASA-class I-II) undergoing day-case laparoscopic cholecystectomy were randomly allocated to receive either total intravenous anesthesia with propofol-remifentanyl (TIVA, n=25) or opioid-free inhalational anesthesia with sevoflurane (GAS, n=25). Five patients (TIVA, n=4, GAS, n=1) were excluded for perioperative surgical reasons. Postoperative data were analyzed for 21 subjects in the TIVA group (mean age 45 years, (range 29-64)), females, n= 20) and 24 patients in the GAS group (mean age 46 years, (range 19-69)), females, n= 20). The gastric emptying study was successful in 18 patients in the TIVA group and 20 patients in the GAS group.

Study III

Ten healthy male volunteers (ASA-class I-II) with a mean age 24 years (range, 19-31) underwent two gastric tone studies on two separate days. Later, analyses of SNP in the MOR gene were performed. Two subjects did not complete the first barostat study (glucagon) and 1 subject did not complete the second barostat study (remifentanyl). Genetic analyses were performed in all subjects (n=9) with successful gastric tone measurements.

Study IV

Gastric myoelectric activity was studied with an electrogastragraph in 20 patients scheduled for elective surgery (ASA-class I-II, mean age 45 years (range, 28-67), females, n=16) and the effect of a bolus dose of fentanyl 1µg/kg was evaluated. Later, genetic analyses of SNP in the MOR gene were performed in 18 of the patients.

Methods

Gastric emptying (I-II)

Gastric emptying was studied with the paracetamol method. (*Acetaminophen* is the name for paracetamol in North America and in the literature the method is also called *the acetaminophen method*). Paracetamol is not absorbed from the stomach, but is rapidly absorbed from the small intestine. Consequently, the rate of gastric emptying determines the rate of absorption of paracetamol administered into the stomach (32).

Paracetamol 1.5 g dissolved in 200 mL of water (at room temperature) was given orally (Study I) or through a nasogastric tube (Study II). Blood samples were taken from an intravenous catheter prior to the administration of paracetamol, at 5, 10, and 15 minutes after administration, and then at 15-minute intervals during a total period of 120 min. Serum paracetamol was determined by an immunologic method including fluorescence polarization (TDx acetaminophen®; Abbott Laboratories, Chicago, IL, USA). Paracetamol concentration curves were produced and the maximal paracetamol concentration ($C_{\max}$), the time taken to reach the maximal concentration ($T_{\max}$), and the area under the serum paracetamol concentration time curves from 0 to 60 minutes (AUC_{60}) and from 0 to 120 minutes (AUC_{120}) were calculated. $T_{\max}$ was assumed to be 120 minutes if no paracetamol was detected in any sample. The paracetamol method is a well-accepted method for studying the liquid phase of gastric emptying, and AUC_{60} correlates well with measures of gastric emptying performed using isotope techniques (32, 153)

Gastric tone (III)

Gastric tone was measured by an electronic barostat (SVS®; Synetics AB, Stockholm, Sweden). The gastric barostat is an instrument with an electronic control system that maintains a constant preset pressure within an air-filled flaccid intragastric bag by momentary changing of the volume of air in the bag (37, 154). When the stomach contracts, the barostat aspirates air to maintain the constant pressure within the bag, and when the stomach relaxes, air is injected. The pressure in the bag was set at 2 mmHg above the basal intragastric pressure. The pressure change at which respiration is perceived on the pressure tracing, without an increase or decrease in the average volume, is the basal intragastric pressure.

The bag, made of ultrathin polyethylene, has a capacity of 900 ml and is connected to the barostat by a double-lumen 16 Ch gastric tube. The barostat measurements followed the recommendations presented in a review article by an international working team and the barostat instrument fulfilled the criteria determined by this group (37).

Before the gastric intubation, propofol 0.3 mg/kg was given for sedation. Previous studies in volunteers have shown that this dose of propofol does not influence gastric tone (155), and it was given at least 30 min before the study started. The intragastric bag was folded carefully around the gastric tube and positioned in the gastric fundus via oral intubation. Thereafter, the gastric bag was unfolded by being slowly inflated with 300 ml of air under controlled pressure (<20mmHg), and the correct position of the bag was verified by traction of the gastric tube. During the measurements, the mean gastric volume during each five-minute interval was calculated.

Electrogastrography (IV)

Electrogastrography (EGG) is the cutaneous recording of gastric myoelectrical activity, and the activity is closely associated with gastric motility (156). Gastric smooth muscles display a rhythmic electrical activity, slow waves, with a frequency of approximately 3 cycles per minute. These slow waves originate from a gastric pacemaker region in the corpus and propagate towards the pylorus. With influence of the enteric nervous system and other regulatory mechanisms, the slow waves trigger the onset of spike potentials, which in turn initiate coordinated contractions of the gastric smooth muscles (12). Gastric motility and emptying depend on these slow waves.

Figure 1.

Electrode placements in electrogastric study: Electrode 3 was placed halfway between the xiphoid process and the umbilicus. Electrode 4 was placed 4 cm to the right of electrode 3. Electrodes 2 and 1 were placed 45 degrees to the upper left of electrode 3, with an interval of 4 to 6 cm. The ground electrode was placed on the left costal margin horizontal to electrode 4. The reference electrode (electrode 0) was placed at the cross point of the horizontal line containing electrode 1 and the vertical line containing electrode 3. (Walldén *et al*, *Acta Anest Scand* 2008. *In Press*.)

Six EGG electrodes were placed on the abdomen after skin preparation. The electrodes consisted of four active electrodes, one reference electrode and one ground electrode, as illustrated in Figure 1. A motion sensor was also attached to the abdomen. We used the Medtronic Polygram NET EGG system (Medtronic A/S, Denmark) for the simultaneous recording of four EGG signals. Our EGG system was configured to accept an electrode impedance of less than 11 k Ω after skin preparation. The EGG signal was sampled at ~105 Hz, and this was downsampled to 1 Hz as part of the acquisition process (157).

All EGG tracings were first examined manually by two of the investigators (JW, GL). Prior to the analysis, motion artifacts in the EGG signal, indicated by the motion sensor, were identified and removed manually. For each patient, the EGG channel with the most typical slow-wave pattern during baseline recording (before fentanyl) was selected for further analysis.

An overall spectrum analysis was performed on each of the two main 30-minute segments (before and after fentanyl, respectively) of the selected channel using the entire time-domain EGG signal (157). Sequential sets of measurement data for 256s with an overlap of 196s were analyzed using fast Fourier transforms and a Hamming window for the calculation of running power spectra. When the entire signal was processed, the power spectra for each segment were combined to arrive at the overall dominant frequency (DF) and power of the dominant frequency (DP).

The EGG segments and the spectral analysis after fentanyl were further classified either as 1) Unaffected EGG (no change in DF after fentanyl), 2) Bradygastric EGG (decrease in DF ≥ 0.3 after fentanyl) or 3) Flatline-EGG (total visual disappearance of a previously clear sinusoidal 3 cpm EGG-curve after fentanyl) (see example in figure 3) without any quantifiable DF. When DF was not quantifiable, DF was set to 0.

Data from the baseline EGG were compared to data from a previous multicenter study in normal subjects (157) to test if the group in study IV was similar to a normal population.

Genetic Analysis (III-IV)

Due to the large interindividual variations in the gastric tone response after remifentanyl, we investigated if this variation could be explained by genetic

variability, polymorphisms, in the μ -opioid receptor gene. After reviewing the literature, we decided to analyze polymorphisms with relative high frequencies and with reports of altered responses. Therefore, we focused on the μ -opioid receptor gene polymorphisms A118G and G691C (128).

DNA collection and purification.

Venous blood (10 ml) was collected from the subjects in EDTA tubes and the samples were stored frozen at -70°C . Genomic DNA was purified from peripheral leukocytes in 1 ml of EDTA blood on a MagNA Pure LC DNA extractor, using the MagNA Pure LC Total Nucleic Acid Isolation Kit – Large Volume (Roche Diagnostics Corporation, Indianapolis, IN, USA).

Genotyping.

Genotyping was performed at CyberGene AB, Huddinge, Sweden. The A118G SNP in Exon 1 and the IVS2 G691C SNP in Intron 2 were genotyped using polymerase chain reaction amplification and sequencing. Oligonucleotide primers (forward: 5'-GCGCTTGGAACCCGAAAAGTC; reverse: 5'-CATTGAG CCTTGGGAGTT) and (forward: 5'-CTAGCTCATGTTGAGAGGTTC; reverse: 5'-CCAGTACCAGGTTGGATGAG) were used for amplifying gene fragments containing Exon 1 and Intron 2, respectively. PCR conditions comprised an initial denaturing step at 95°C for 1 min followed by 30 cycles at 94°C for 1 min, annealing at $47.2\text{--}53.4^{\circ}\text{C}$ (depending on primer) for 1 min and extension at 68°C for 3 min, and a final extension at 68°C for 3 min. The amplified fragments were sequenced using the same primers with the addition of Rev 1-2 5'-TTAAGCCGCTGAACCCCTCCG and the BigDye Terminator v1.1 Cycle Sequence Kit (Applied Biosystems, Foster City, CA, USA). PCR amplification and sequence reactions were done on ABI GeneAmp 2400 and 9700 (Applied Biosystems). Sequence analysis was first done on MegaBACE 1000 (Amersham Biosciences, CA, USA) and then confirmed with ABI 377XL (Applied Biosystems).

Procedure

Study I

In a randomized order, gastric emptying was studied on four occasions in each subject, with at least 1 day between occasions. The subjects were given a continuous infusion of remifentanyl on two occasions while lying either on the right lateral side with the bed in a 20° head-up position (RHU) or on the left lateral side with the bed in a 20° head-down position (LHD). On the other two occasions, no remifentanyl infusion was given, and the subjects were studied lying in the two positions.

All subjects fasted for at least 6 h before each study. For the two occasions with remifentanyl, remifentanyl was given as a continuous intravenous infusion in a dose of $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and was started 10 minutes before the ingestion of paracetamol. The infusion was terminated directly after the last blood sample (120 min) was drawn.

Study II

All patients fasted according to clinical guidelines (107) and were premedicated with midazolam 1-2 mg I.V. Before induction, all patients received ketorolac 30 mg I.V. In the TIVA group, anesthesia was induced with an infusion of remifentanyl $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, followed after 2 minutes by a target-controlled infusion (TCI) of propofol at $4 \mu\text{g} \cdot \text{mL}^{-1}$ (induction time 60 seconds). In the GAS group anesthesia was induced with 8 % sevoflurane via a facial mask. After attaining an adequate level of anesthesia, muscular relaxation was obtained in both groups with rocuronium $0.6 \text{ mg} \cdot \text{kg}^{-1}$ IV and the trachea was intubated after 90 seconds. In the TIVA group anesthesia was maintained with remifentanyl $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and TCI propofol adjusted ($2\text{-}4 \mu\text{g} \cdot \text{mL}^{-1}$) to maintain a BIS-index below 50. In the GAS group anesthesia was maintained with sevoflurane, adjusted to maintain a BIS-below 50. No prophylactic antiemetics were given. A nasogastric tube was placed in all patients during anesthesia. At the end of surgery, 20 mL of 0.25% levobupivacaine was infiltrated at the insertion sites of the laparoscopic instruments, muscular relaxation was reversed with neostigmine $2.5 \text{ mg/glycopyrrolate } 0.5 \text{ mg}$, and anesthetic agent(s) were terminated. The patients were extubated in the operating room after return of consciousness and spontaneous breathing and transferred to the adjacent day-care unit for recovery. Except for the continuous infusion of remifentanyl in the TIVA group, no opioids were given during anesthesia. The gastric emptying study measurement was initiated immediately after arrival in the day-care unit.

Patients stayed in the day-care unit for at least 4 hours and PONV and pain parameters were evaluated every hour. After discharge, patients received a questionnaire regarding the postoperative 4-24 hour-period, and they rated their maximal pain and maximal nausea and were questioned about vomiting. In addition, a telephone interview was performed on the first postoperative day. Combining the results, we received postoperative data on PONV, maximal VAS-score for pain, and time to first postoperative opioid analgesic for the time periods 0-2 hours and 2-24 hours postoperatively.

Study III

All subjects fasted for at least 6 h before each study. Each subject underwent two study protocols on two separate days. Before the gastric intubation the subjects received a bolus dose of propofol (0.3 mg/kg IV). In the first study, the effect of glucagon on gastric tone was measured. In the second study, gastric tone was measured during and after a remifentanyl infusion and, after a washout-time of 30 minutes, during readministration of remifentanyl in combination with glucagon. The study protocol is illustrated in Figure 2.

During study situations, vital parameters, blood-glucose, nausea and any other symptoms were recorded.

Later, subjects (n=9) were asked to participate in the genetic analysis of the MOR gene and we obtained blood samples.

Figure 2
Schematic illustration of the study protocol in study III.

Glucagon Study

Remifentanyl Study

Study IV

The study was performed in a pre-anesthesia area before the induction of anesthesia. Patients fasted for at least 6 hours from solid foods and 2 hours from clear fluids. No premedication was given. While the patient was lying in a comfortable bed rest position, an intravenous line was inserted and the EGG recordings were initiated. After achieving a stable EGG signal, a 30-minute baseline EGG recording was collected. Without discontinuation of the EGG recording, 1 $\mu\text{gram}\cdot\text{kg}^{-1}$ of fentanyl was given as an intravenous bolus through the intravenous line and the EGG recording continued for another 30 minutes. Charts and notes from the recovery unit were reviewed and we collected data regarding analgesic and antiemetic requirements.

Later, patients were asked to participate in the genetic analysis of the MOR gene and we obtained blood samples.

Statistics

The significance level was set at 5% in all tests. Data are presented as means (SD) or medians (ranges).

In study I, repeated-measures analysis of variance was used for overall differences between the study situations. If the analysis of variance showed differences, a paired Student's t-test with Bonferroni Correction was performed between the study situations.

In study II, the unpaired Student's t-test was used for comparisons between the groups of primary outcome variables. For the secondary outcome variables, the unpaired Student's t-test, the Mann Whitney U test or Fisher's exact test were used.

In study III, repeated-measures analysis of variance was used for overall changes in gastric tone over time. For comparisons between time periods, Fisher's PLSD was used.

In study IV, Wilcoxon's signed rank test and the 95% confidence interval for the difference between the medians were used for analysis of the primary EGG outcome variables. The unpaired t-test was used for the comparison of baseline EGG data with the historical controls. Fisher's exact test was used to test associations between PONV parameters and EGG outcome.

Results

Gastric emptying during an infusion of remifentanil and the influence of posture (I).

Infusion of remifentanil delayed gastric emptying. During the control situations there were differences in gastric emptying variables between the two extreme positions, but there were no differences during the infusion of remifentanil (Table 1 and Figure 3). In three subjects, the dose of remifentanil had to be reduced due to side effects.

Immediate postoperative gastric emptying after total intravenous remifentanil-propofol based anesthesia (II).

There were no differences in postoperative gastric emptying between the TIVA group and the GAS group. Both groups differed significantly from a pooled historical control group. However, there was great variability within both study groups (Table 1 and Figure 4).

Table 1.
Gastric emptying variables in study I and study II.

	AUC60	Cmax	Tmax
	min $\mu\text{mol mL}^{-1}$	$\mu\text{mol mL}^{-1}$	min
Study I (n=10)			
Control RHU	5092 (1125)	138 (45)	25 (14)
Control LHD	3793 (1307)	94 (30)	47 (22)
Remifentanil RHU	962 (902)	34 (24)	94 (33)
Remifentanil LHD	197 (128)	16 (14)	109 (10)
Study II			
TIVA (n=18)	2458 (2775)	71 (61)	53 (55)
GAS (n=20)	2059 (2633)	81 (37)	83 (41)
Historical controls (n=36)	5988 (1713)	155 (46)	29 (15)
<i>Paired T-test with Bonferroni Correction</i>			
RHU-Remi vs RHU-Control	p<0.0001	p< 0.0001	p<0.0001
RHU-Remi vs LHD-Remi	NS	NS	NS
RHU-Remi vs LHD-Control	p<0.0001	p < 0.0001	p<0.0001
RHU-Control vs LHD-Remi	p<0.0001	p < 0.0001	p<0.0001
RHU-Control vs LHD-Control	p<0.0083	p <0.0083	NS
LHD-Remi vs LHD-Control	p < 0.0001	p<0.0001	p<0.0001
<i>Unpaired t-test</i>			
TIVA vs GAS	NS	NS	NS
TIVA vs Historical Controls	p<0.001	p<0.001	p<0.001
GAS vs Historical Controls	p<0.001	p<0.001	p<0.001

Figure 3
Gastric emptying in study I. Mean (SD) concentrations of paracetamol over time.

Figure 4
Gastric emptying in study II. Mean (SD) concentrations of paracetamol over time.

Gastric tone after injection of glucagon (III)

Glucagon decreased gastric tone in all subjects during the glucagon study. During the remifentanyl study and the ongoing remifentanyl infusion, only one subject had a decrease in gastric tone after the injection of glucagon, while the others were almost unaffected. (Figure 5).

Gastric tone during an infusion of remifentanyl (III)

There were distinct responses in gastric tone during the remifentanyl infusion. However, the responses were variable. Four subjects responded to remifentanyl with a marked increase in gastric tone (decreased volume in bag) that returned to baseline levels during washout. Four subjects responded to remifentanyl with a marked decrease in gastric tone (increased volume) and maintained a low gastric tone during the washout period. In one subject (no. 5) gastric tone was almost unaffected. The mean gastric tone was significantly lower during the washout period than before starting the infusion. During the readministration of remifentanyl, there were increases in gastric tone among subjects who increased in tone during the previous remifentanyl infusion. The subject with unaffected gastric tone during the previous infusion increased in gastric tone. The subjects who maintained a low gastric tone during washout continued to maintain a low gastric tone. (Figure 5)

Figure 5.
Individual gastric volumes in the barostat study (III).

Electrogastrography (IV)

Compared to historical controls (157), there were no differences in the baseline EGG variables.

After the administration of intravenous fentanyl, there was a significant reduction in both the dominant frequency (DF) and the dominant power (DP) of the EGG spectra (Figure 7).

Among patients with a flatline-EGG ($n=6$), the median (range) time from the administration of intravenous fentanyl to the observed disappearance of the slow waves was 5 (1-9) minutes. In 5 of these patients, there was reappearance of the 3 cpm slow-wave EGG pattern 30 (29-35) minutes after the administration of fentanyl.

There was large variation between patients in the response to intravenous fentanyl. EGG recordings were unaffected in 8 patients, 5 patients developed a slower DF (bradYGastria) and in 6 patients the slow-wave tracings disappeared totally (flatline-EGG). For an illustration of the effect, see Figure 6.

Figure 6.
An individual electrogastrographic response to Fentanyl.

Figure 7.

Changes in the dominant frequency (DF) and the dominant power (DP) of the electrogastrographic spectra after Fentanyl. (Walldén et al. *Acta Anesth Scand*, 2008. *In Press*)

Genetic study (III-IV)

We found no association between the variable outcome in studies III and IV and the presence of SNP A118G or G691C in the MOR (Table 2).

Table 2.

Results from the determinations of SNPs in the MOR gene with correlations to outcome groups in studies III and IV.

	<u>118 A>G genotype</u>			<u>IVS2 + 691 G>C genotype</u>		
	Wild Type (AA)	Hetero-zygous (AG)	Variant (GG)	Wild Type (GG)	Hetero-zygous (GC)	Variant (CC)
<i>Study III</i>	<i>n=7</i>	<i>n=2</i>	<i>n=0</i>	<i>n=5</i>	<i>n=2</i>	<i>n=1</i>
Increased tone (n=4)	4			3	1	
Unchanged tone (n=1)		1		1		
Decreased tone (n=4)	3	1		1	2	1
<i>Study IV</i>	<i>n=15</i>	<i>n=2</i>	<i>n=1</i>	<i>n=0</i>	<i>n=14</i>	<i>n=4</i>
Unaffected EGG (n=6)	5	1			6	
Bradycastria (n=5)	4		1		2	3
Flatline (n=6)	5	1			5	1
Excluded from the EGG-analysis (n=1)	1				1	

No associations found between presence of polymorphism and gastric outcome (Chi-Square tests).

PONV (I-IV), other side effects (I-IV) and postoperative pain (II).

In study I, six subjects experienced nausea, three subjects vomited and six subjects had pruritus during infusion of remifentanyl. Seven subjects experienced

dysphagia during remifentanil and five subjects complained of headache during and/or after the infusion of remifentanil.

In study II, the postoperative incidence of nausea and vomiting was high. During the 0-24 h postoperative period, 16 patients (76%) in the TIVA group and 20 (83%) patients in the GAS group experienced PONV symptoms. However, there were no significant differences between the groups. There were shorter times to rescue analgesics in the TIVA group (median 17 minutes) compared to the GAS group (median 44 minutes).

In study III, 62% (n=5) of the subjects experienced nausea during the glucagon experiment. During remifentanil, 33% (n=3) experienced nausea and 66% (n=6) had nausea with the combination of remifentanil and glucagon. Further, during remifentanil, 77% (n=7) had pruritus, 33% (n=3) had headache and 22% (n=2) reported dysphagia.

In study IV, the incidence of PONV in the recovery unit was 53% (n=10) and there was a need for rescue antiemetics in 47% (n=9) of the patients. We found an association between flatline/bradycardic ECG and the requirement for rescue analgesics ($P=0.02$).

Discussion

In this thesis I have studied the physiologic effects of opioid drugs on gastric motility using both standard and novel methods. With the genetic analyses of the μ -opioid receptor gene, I have introduced new aspects in the field of opioid induced gastrointestinal motility disturbances.

As expected, opioids had a pronounced effect on gastric motility. Gastric emptying was delayed, gastric tone altered and there were changes in the EGG recordings. However, there was great interindividual variability and the variability could not be explained by genetic variations in the μ -opioid receptor. Further, we found no difference in postoperative gastric emptying between an opioid based and opioid free anesthesia, and we suggest that other factors than opioids contribute to affecting gastric motility.

The Paracetamol method

In studies I-II we used the paracetamol method to study the liquid phase of gastric emptying. Paracetamol is absorbed in the proximal part of the small intestine, and as gastric emptying is considered the rate limiting step in the absorption profile, variables calculated from the paracetamol plasma concentration curve can be used to describe the emptying rate from the stomach (33). Nimmo et al showed in 1975 that the area under the concentration curve during the first 60 minutes (AUC60) correlated well with “gold standard” scintigraphic methods (32). A recent systematic review concluded that the paracetamol method is well correlated to scintigraphic assessments of gastric emptying (153), and in our studies we used the validated variables AUC60, AUC120, T_{max} and C_{max} to describe gastric emptying. However, it has been suggested that other variables might be even more accurate, i.e. the ratio between concentrations at two time points, $C(2t)/C(t)$ or the ratio between two AUC at two time points. Then only absorption and elimination constants influence the results, and differences between individuals in volume of distribution, dose and first-pass metabolism are eliminated (153, 158). It might be valuable to add these variables in future studies. Also, the use of a salivary instead of a venous sample for the measurement of paracetamol has been proposed, but the method still needs validation (159). There are also suggestions that studies with the paracetamol method should be done with crossover designs to reduce the influence of variability between individuals in pharmacokinetic parameters (158). This might be taken

into account in experimental studies, but it would be difficult in clinical postoperative studies as the surgical procedure cannot be repeated.

The paracetamol method is a simple and cheap bedside method for the evaluation of gastric emptying, but it is important to remember that it is an indirect quantification of gastric emptying with limitations regarding interpretation.

Gastric barostat

In study III we used the gastric barostat for the measurement of proximal gastric tone. It could be difficult to understand the concept of gastric tone, and it is therefore important to distinguish it from gastric pressure. The smooth muscles in the proximal stomach have the ability to generate a constant contraction (also called a tonic contraction) and with that contraction the gastric wall applies a certain pressure to the intraluminal contents. As the stomach adapts for volume loads, the smooth muscles are elongated through diminished contraction and the intraluminal pressure is maintained. This regulation with sustained muscular activity is referred to as gastric tone (8), and to simplify, changes in gastric tone are changes in the length of the smooth muscles.

The gastric barostat is the standard method for the evaluation of gastric tone, and there are currently no other good methods available. The technique is invasive and involves the introduction of a bag into the stomach (160), and this might interfere with the response. However, the bag resembles a load of food and we can consider it as partly physiological. The gastric barostat method is most commonly used in research regarding the accommodation response, i.e. in the field of dyspepsia, and usually subjective discomfort and compliance are evaluated while the bag in the proximal stomach is distended (37, 160). It is important to point out that we did not perform any distension tests and that we did not study the accommodation response. We maintained a fixed, relatively low pressure in the bag and studied effects of an opioid on gastric tone at a specific pressure level. It might be interesting to perform distension tests with opioids, but we consider this difficult with remifentanyl and other potent opioids as their analgesic effects blunt the perceptions and might harm the stomach if pressure is elevated too high.

We found great variability in gastric tone during the remifentanyl infusion. We do not believe this was due to a methodological problem with the gastric barostat. During the glucagon part of the study all subjects responded with a clear decrease

in tone (increased volume). This validates that the gastric barostat was working properly, since an expected relaxant stimulus, glucagon, decreased the tone in all subjects. Also, the same barostat equipment and setup were used in previous studies by our group (84, 155) and we did not observe this kind of variation.

Electrogastrography (EGG)

In study IV we used cutaneous electrogastrography to study gastric myoelectric activity. This activity is characterized as a constant ongoing fluctuation of the membrane potential in the syncytium of the gastric smooth muscle cells. Specialized smooth muscle cells without contractile properties, interstitial cells of Cajal (ICC), are responsible for the distribution and propagation of the electric activity. The pace of the fluctuations is normally determined by ICCs in the corpus region, and the electric potential is propagated distally. These electrical fluctuations are called gastric slow waves and they usually have a frequency of about 3 cycles per minute. (156, 157, 161-163) The fluctuations per se do not initiate muscular contraction, as the electrical potential is below the contraction threshold. Excitatory stimuli from the controlling enteric network must be present to initiate spike potentials and contractions (12). With the slow waves, the pulse and propagation of the propulsive contractions are controlled.

Cutaneous EGG is the summation of electrical potentials from the gastric muscle in a specific axis. This must be distinguished from electromyographic tracings with electrodes inserted into the gastric wall; in that case the electrical potential at a fixed point is measured. After our intervention, we found a lower frequency in the slow waves and also a disappearance of the waves. The physiological explanation for the bradygastria might either be a reduction in the frequency of the pacesetter cells in the corpus *or* that normal pacesetter ICCs are “knocked-out” and the slow waves are controlled by more distal ICCs with slower intrinsic frequency (156). Further, the disappearance of the slow waves might reflect a disappearance of the oscillations in membrane potential *or* a total disorganization of the spontaneous activity. The latter might be more likely, as antral tachygastria, leading to a functional uncoupling of the slow waves, has been observed after opioid administration (66), and gastric arrhythmias are generally caused by disruptions of the slow waves(164). Our study is one of the first to use the EGG in the perioperative setting. We suggest that the method should be used more frequently, as it measures changes in gastric myoelectric activity, and this might help us to understand the pathology behind the opioid induced impairments of gastric myoelectric activity.

Genetic testing

Genetic evaluation of the μ -opioid receptor gene was done in studies III and IV. The findings included major interindividual variability in motility variables in subjects receiving opioids. Recent reports have suggested that SNPs in the MOR gene can alter the effects of opioids (129, 165), and to our knowledge there is no previous work where the issue is explored in the context of gastrointestinal motility. Therefore, we collected blood samples from subjects who participated in the studies. Genetic analysis was done by a contracted laboratory using routine molecular biological techniques. Hence, we are the first to evaluate a possible association between opioid effects on gastrointestinal motility and genetic variations in the MOR.

Gastric emptying during a remifentanil infusion and influence of posture (I)

In Study I we evaluated the effect of posture on gastric emptying and the objectives were in part to evaluate pyloric function. If gastric contents are passively directed towards the pylorus, gastric emptying would be facilitated in states of normal motility *or* when the pyloric sphincter is abnormally relaxed. We used two extreme body positions in our study protocol – the RHU-position where contents theoretically are directed towards the pylorus, and the LHD-position where contents are directed from the pylorus. During the control situations, gastric emptying was better in the RHU-position. This is in agreement with other studies where body positions that direct stomach contents towards the pylorus facilitate gastric emptying (25-27, 166). During the remifentanil infusion, gastric emptying was delayed in both positions compared to the control situations. This confirms that remifentanil has the same ability as other MOR agonists to affect gastric motility and delay gastric emptying (32, 67, 68, 88, 167). However, we found no significant differences between the positions. This indicates that remifentanil increases pyloric tone and thereby impairs the flow out to the duodenum.

Gastric emptying after opioid based vs opioid free anesthesia (II)

In study II we compared gastric emptying in two anesthetic protocols, one with the opioid remifentanil and the other without opioids. We hypothesized that if perioperative opioids play a major role in the postoperative inhibition of gastric motility, there would be differences between the groups. The results showed that gastric emptying was delayed in both groups compared to pooled data from historical controls. However, we could not find any significant differences between the groups. This indicates that the use of remifentanil during anesthesia

impairs postoperative gastric emptying in the same way as a solely inhalational anesthesia.

Interestingly, if the figures are compared to the gastric emptying rates during the remifentanyl infusion in Study I, gastric emptying was better in Study II. A reasonable assumption is that gastric motility during anesthesia with remifentanyl would be affected at least in the same way as during the remifentanyl experiments. As the measure of gastric emptying in study II was done after the cessation of anesthesia, the results indicate that the inhibitory effect of remifentanyl on gastric emptying was reduced quickly. At the time when we measured gastric emptying in Study II, the opioid effect might no longer have been present and other factors might have contributed to the delay. The surgical trauma per se delays gastric motility (1, 2, 4, 168), and if this factor plays the major role, then there would be no differences between the groups.

There is limited knowledge about the effect on gastric motility of the other anesthetics used in our protocols. Propofol in higher doses might inhibit motility (80), and volatile agents inhibit motility with an effect that ceases quickly after termination of the agents (76-78). Remifentanyl and volatile agents might therefore be considered similar regarding the time course of the gastric inhibition, and that might also explain the finding of no difference. Future studies must compare remifentanyl with other potent opioids and evaluate if postoperative gastric emptying is enhanced with remifentanyl. As an early oral intake is preferred today, the choice of a perioperative opioid with minimal impact on postoperative gastric motility could be of importance.

Furthermore, there was great variability in the gastric emptying rates within the groups, and both groups had patients with normal gastric emptying and patients with no gastric emptying at all. As patients received IV opioids for severe pain during recovery, we tested whether there was any association between opioid analgesia during recovery and gastric emptying rates, but we found no association. The variability must be related to other factors.

Effects of remifentanyl on gastric tone (III)

In study III we evaluated changes in gastric tone during an IV infusion of remifentanyl. We found that remifentanyl had a marked effect on gastric tone, but there were two distinctly different patterns of reactions, with about half of the subjects increasing in gastric tone (decreased volume) and about half of the

subjects decreasing in gastric tone (increased volume). Due to this variability, we were not able to statistically prove the response during remifentanyl. However, the gastric tone was statistically lower (higher volume) after the infusion of remifentanyl compared to the baseline period. We believe these are important findings, as they show that opioid effects on human gastric motility are variable and complex.

Proximal gastric tone is an important part of gastric motility and it is mainly controlled by the autonomous nerve system. Vagal cholinergic nerves mediate excitation (contraction) while vagal non-cholinergic non-adrenergic (NANC) nerves mediate inhibition (relaxation) (169). Recent studies have identified nitrous oxide as one of the main transmitters in the NANC pathway. In humans, the NANC pathway is believed to be silent during fasting conditions and activated on volume load by the adaptive reflex (170). In addition, there are sympathetic adrenergic spinal nerves that inhibit motility mainly through cholinergic inhibition (17).

Several animal studies have tried to identify targets for the opioid induced inhibition of gastric motility. It is widely believed that μ -opioid receptor (MOR) agonists inhibit the release of Ach in the stomach (61), and there is also evidence that MOR agonists reduce the relaxation induced by the NANC pathway (171). Opioids might also have direct excitatory effects on gastric smooth muscles (51). Opioids also act in the central nervous system (CNS). There is evidence that MORs are present on and inhibit excitatory neurons projecting to gastrointestinal motor neurons in the dorsal motor complex (DMV) of the medulla (69). In this way activation of central MORs inhibits the excitatory vagal output, leading to inhibition of intestinal transit and induction of gastric relaxation in animal models. In humans, there is evidence that opioids inhibit gastric motility through a central mechanism (66).

Hence, depending on the current state of autonomous and enteric nerve systems and the main effect site, opioids have the potential to both increase and decrease gastric tone.

There are diverging results in the literature regarding the effects of opioids on gastric tone in humans. Penagini found that morphine increased gastric tone (172), while Hammas reported a decrease in gastric tone (155). Both studies used the same dose of intravenous morphine (0.1 mg/kg) and both used a gastric

barostat. However, there were important differences between the studies. In the first study, baseline gastric tone was set to resemble a gastric load of a meal, and in the second study baseline was set to fasting conditions. The stomach wall was probably more distended (higher volumes in the intragastric bag) before morphine in Penagini's study compared to Hammas' study, resulting in an activated adaptive reflex. This leads to completely different baseline conditions. In Penagini's subjects there were probably low cholinergic and high NANC vagal inputs to the stomach, and the reverse baseline conditions were probably present in Hammas' subjects. This might explain why a MOR antagonist contracted the stomach (through NANC inhibition) in one study and relaxed the stomach (through cholinergic inhibition) in the other study.

An interesting finding in Hammas' study was that the concurrent administration of propofol altered the effect of morphine on gastric tone. Propofol *per se* had no effect on gastric tone, but after the subsequent administration of morphine, gastric tone increased (volume decreased), contrary to the response to morphine alone. We cannot explain the mechanism behind this modulation, but there is evidence for central interactions and modulations between GABAergic and opioid pathways (47). Other types of modulations of gastric tone have also been described; in animals with an intact vagus nerve, noradrenaline relaxed the proximal stomach while vagotomy reversed this response (169).

Can we explain the variable responses seen in our study within this context? Remifentanyl is a potent MOR agonist and the effect sites are probably both at the stomach level and in the CNS. We speculate that the "normal" opioid response during fasting conditions, as seen in Hammas' study, is a decreased cholinergic activity resulting in a decrease in gastric tone. However, due to the high potency of remifentanyl, direct smooth muscle effects might predominate in some subjects, resulting in an increase in tone. Like propofol, remifentanyl might also have properties that modulate the opioid response. The focus of these speculations is that opioid effects on gastric tone are variable and depend on factors like the state of the subject and the current status of the neural pathways and smooth muscles that are involved. This might be an explanation for the variable results in study III.

Effects of fentanyl on gastric myoelectrical activity (IV)

In study IV we evaluated how fentanyl affected gastric myoelectrical activity. Before the intervention, all subjects had a 3 cpm slow wave activity, which did

not differ from a recent multicenter electrogastrography study in normal subjects (157). After fentanyl, gastric myoelectrical activity was inhibited, with a decrease in both the dominant frequency and the dominant power of the electrogastrographic spectra. The electrical activity was disrupted after the administration of fentanyl, and we observed both bradygastria and disappearance of the slow wave activity. However, the EGG was unaffected in about half of the subjects.

There are only a few reports in the literature regarding the effects of opioids on gastric electrical activity. Invasive recordings of gastric myoelectrical activity have shown that morphine transiently distorts the slow-wave activity and initiates migrating myoelectric complexes (65, 173). Cutaneous recordings with EGG have shown that morphine induces tachygastria (66). The shift in the basal EGG frequency towards bradygastria that we observed in some of the subjects indicates that opioids inhibit the ICC-network. Bradygastria is believed to be a decrease in the frequency of the normal pacemaker cells, while other dysrhythmias like tachygastria have ectopic origins in the stomach (174).

We tried to explain the variability seen in responders and non-responders. One hypothesis may be a difference between the individuals in the plasma concentration of fentanyl. Unfortunately, blood samples were not collected during the EGG study. By using a pharmacokinetic model (53, 175), we calculated the predicted plasma concentrations of fentanyl for each subject. We were not able to find any differences in the predicted concentrations between the outcome groups. However, there is a notable wide variability in the model that may conceal relevant differences. Further, as body composition affects the pharmacokinetic profiles of a drug, we tested for differences in body weight and body mass index between the groups, but found no differences. Also, it cannot be ruled out that differences between the subjects in pharmacokinetic factors, i.e. distribution volume, metabolism and clearance, alter the effect-site concentration of fentanyl and thus the effect on gastric motility.

With the knowledge we have today, we cannot determine the exact mechanism of the inhibition of myoelectrical activity. Possible locations of opioid receptors are the interstitial cells of Cajal, interneurons in the enteric nervous system, and nerve terminals from ascending pathways. There might also be a direct effect on gastric smooth muscles, but such an effect would probably not affect the slow waves.

Our findings confirm that opioids inhibit the electrical activity, but we cannot explain the variable outcome.

Associations to genetic factors (III, IV).

We hypothesized that genetic variability in the MOR gene was responsible for the variations seen in the barostat and EGG studies (III and IV), but we did not find such an association.

There are data indicating that genetic differences are able to alter the gastrointestinal response to opioids. The variable analgesic effect of codeine is related to genetic variations, leading to different expressions of the enzyme (CYP2D6) that metabolizes codeine to morphine. Among extensive metabolizers, orocecal transit time is prolonged compared to poor metabolizers and correlates to higher morphine concentrations in plasma (176). To our knowledge, there are no studies regarding the relation of SNP in the μ -opioid receptor to the effect of opioids on gastrointestinal motility. After reviewing the literature, we decided to analyze two common SNPs in the μ -opioid receptor gene - A118G and IVS2 G691C (128).

The frequencies of SNP A118G in our material were similar to the frequencies reported in the literature, and the distributions were in Hardy-Weinberg equilibrium. There were discrepancies in the distributions of SNP G691C between studies III and IV. In study III, the distribution was in equilibrium. In study IV, all investigated subjects were either heterozygote or homozygote to G691C and there were no normal “wild types” of G691C, and the distribution was not consistent with the expected distributions in Hardy-Weinberg equilibrium. Our study group may not represent a normal population, as the majority of subjects were woman and almost all of them had gallbladder disease. This may introduce a selection bias. However, with the small sample size it is difficult to draw any conclusions regarding the distribution.

Our results indicate that pharmacogenetic differences in the opioid receptor gene may not be a major factor regarding the variable gastric outcome caused by an opioid. However, due to the small sample size we want to emphasize that our results are preliminary observations and they must be interpreted with caution. Genetic variations can still be one co-factor, but not the factor that determined the outcome in our studies.

Side effects of opioids

Nausea and vomiting are known side effects of opioid treatment (177) and we had a high incidence in our studies. In the studies with volunteers (I and III), one third to one half of the subjects experienced nausea during the remifentanyl infusion. The incidences of PONV in study II were 48% and 62% (TIVA and GAS), respectively, and in study II the incidence was around 50%.

Those in Study I who experienced nausea did so during both occasions with remifentanyl. This indicates that there are individual factors that do not change over time that determine if opioids induce nausea. In study IV we found an association between opioid induced EGG changes and PONV. We speculate that in subjects who are sensitive to opioids, both gastric motility changes and nausea are easily induced. The emetic center and the motor nuclei are located close to each other in the medulla and neurons influenced by opioids might affect both systems.

In studies I and III, subjects experienced difficulties swallowing during the remifentanyl infusion. There are reports in the literature showing that potent opioids can cause dysphagia (178). This side effect provides evidence that potent opioids inhibit motility patterns through central mechanisms, as swallowing is a process controlled by neuronal networks in the medulla (179).

Future perspectives

As we still have only small islands of knowledge about the actions of opioids in the gastrointestinal system and the underlying mechanisms (7), more research is needed to find out how we can diminish the side effects of the opioids. Novel, peripheral-acting opioid antagonists are promising and need more evaluation. However, as opioids also act through central mechanisms in the brain (66), it might be impossible to antagonize all side effects in the gastrointestinal tract. Using the results from our studies as a base, we might be able to further explore the efficiency of the new antagonists. Can we improve gastric emptying during opioid treatment? How is the dual response we achieved in gastric tone altered, and can we reveal peripheral and central actions of opioids?

The finding that EGG changes predicted PONV might be useful in helping us identify subjects at high risk for PONV. Properly designed studies must be conducted with this issue as the primary hypothesis.

Conclusions

- Remifentanyl delayed gastric emptying.
- Posture did not influence gastric emptying rates during a remifentanyl infusion.
- There were no differences in postoperative gastric emptying rates between a remifentanyl-propofol based total intravenous anesthesia and an opioid free sevoflurane inhalational anesthesia.
- Remifentanyl both increased and decreased proximal gastric tone and the responses were individual.
- Fentanyl inhibited gastric myoelectrical activity, although half of the subjects were “non-responders.”
- “Responders” to fentanyl (EGG changes) had higher incidences of PONV.
- No associations were found between common SNPs in the μ -opioidreceptor gene and the variable outcomes in the gastric barostat studies and the EGG studies.

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